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ENVIRONMENTAL HAZARD ASSESSMENT REPORT: HIGHER BENZENEPOLYCARBOXYLATES

Frank J. Letkiewicz

Environmental Protection Agency
Washington, D. C.

November 1975

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This report is an analysis of available information on the higher benzenepolycarboxylates (i.e., benzenecarboxylates through benzenehexacarboxylate) pertinent to an assessment of the potential environmental hazard posed by these compounds. Aspects discussed are production and uses of the subject compounds, environmental aspects and biological aspects. The study concludes that current uses of these compounds do not present an environmental hazard, but makes recommendations for additional studies to be undertaken prior to initiation of new and potentially dispersive uses.

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ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

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Higher Benzenepolycarboxylates

Prepared by

Office of Toxic Substances
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PREFACE

Our society uses thousands of chemical substances with many of them released into the environment in varying quantities as production or handling losses, as waste materials, or as a direct consequence of intended or unintended uses. Concern over possible effects of these chemicals has prompted the establishment of a program by the Early Warning Branch of The Office of Toxic Substances to review release, exposure, and effects data to assist in setting priorities for further study or possible regulatory action.

Detailed analyses on every commercial chemical are not practical. Selected materials are initially screened by a simple literature search and a limited number of these chemicals are selected for more detailed study . Criteria for this selection include volume of production, manner of use, market growth potential, exposure patterns, detection in the environment, known toxic effects, and functional or chemical relationships to known environmental pollutants. The early warning system, which first brings chemicals to the attention of the program uses diverse sources, including opinions of experts, referrals from other units of government, reports in the scientific and trade literature, predictive modelling, and public inquiries. Much of the initiative for this study was stimulated by the recently proposed new use of the higher benzenepolycarboxylates as detergent builders in nitrogen- and phosphorous-free formulations. The potential for widespread environmental release from such a use was a real concern.

These hazard assessments are prepared from reviews of the subject substances supplemented by additional searches and inquiries to obtain the most complete and recent information available. Only data considered pertinent to an assessment of environmental hazard are reported in this series.

Although the assessment uses as complete an information base as possible, additional information may be available or may become available. Therefore, these assessments are subject to revisions. The Office of Toxic Substances would welcome any additional pertinent data.

Recommendations in this document are those of the Office of Toxic Substances and may not represent an Agency consensus. Nor do they represent commitment to further action by the Environmental Protection Agency or any other organization. Mention of tradenames and manufacturers of specific products in this document is for purposes of clarity and specificity only and does not constitute an endorsement of any product.

This report was written by Frank J. Letkiewicz. The Environmental Hazard Assessment Series is being prepared under the guidance of Dr. Farley Fisher, Chief of the Early Warning Branch, Office of Toxic Substances.

The literature review which preceded this assessment was conducted by Dr. Philip Howard and Mr. Patrick Durkin of the Syracuse University Research Corporation, Syracuse, New York. That review was supplemented by consultations with selected knowledgeable individuals both within and outside the Federal Government and is part of a report entitled Preliminary Environmental Hazard Assessment of Chlorinated Naphthalenes, Silicones, Fluorocarbons, Benzenepolycarboxylates and Chlorophenols, available through the National Technical Information Service, Springfield, Virginia 22151 (NTIS accession number - PB-238 074/AS).

Appreciation is expressed to the many individuals who provided information and reviewed drafts of this report. Special appreciation is expressed to the Office of Toxic Substances staff and to Dr. M. Schnitzer of the Soil Research Institute, Central Experimental Farm, Canada, for exchanges on the occurrence of benzenepolycarboxylates in soil humic substances. Additional technical reviews, comments and suggestions incorporated into this report were contributed by Dr. Delbert S. Barth, Director, EPA/NERC-Las Vegas; Robert E. McGaughy, EPA Office of

Research and Development, Health Effects Division, Washington, D.C.; Dr. Norman R. Glass, Director, National Ecological Research Laboratory, EPA/NERC-Corvallis; Dr. Donald I. Mount, Director, EPA National Water Quality Laboratory, Duluth; Dr. Charles F. Jelinek, FDA, Bureau of Foods, Division of Chemical Technology, Washington, D.C.; Joan Davenport, Acting Director, EPA Office of Enforcement and General Counsel, Office of Technical Analysis; and Dr. Lawrence A. Plumlee, Medical Science Advisor, EPA Office of Research and Development.

CONCLUSIONS AND RECOMMENDATIONS

Available data on the toxicity and ecological effects and on the levels of environmental exposure to the higher benzenepolycarboxylates are insufficient to assess adequately the hazards to man and the environment posed by these chemicals. Since current uses of and practices concerning these chemicals do not result in significant losses to the environment, attempts to gather these data cannot be justified at this time; such attempts should be made if a new use or practice begins to disperse the chemical to the environment. Specific information which would be needed includes:

1. Environmental fate, degradation, products formed, and the extent to which the compounds are incorporated into humic substances;
2. Health effects resulting from chronic exposure to the compounds if they are not readily degraded or incorporated into humic substances; and
3. Health effects of any degradation products.

SUMMARY OF TECHNICAL ASPECTS

The higher benzenepolycarboxylates, as defined herein, are the benzenetricarboxylates through benzenehexacarboxylate. Only three members of this group of compounds have reported commercial uses, but no detailed production figures are available. Trimellitic anhydride (benzene-1,2,4-tricarboxylic acid, 1,2-anhydride) is used to produce plasticizers, various resins, dyes, and other chemical intermediates. Trimesic acid (benzene-1,3,5-tricarboxylic acid) is currently used as a crosslinking agent in solid propellant fuels. Pyromellitic dianhydride (benzene-1,2,4,5-tetracarboxylic acid, dianhydride) is used as a crosslinking agent and curing agent for epoxy resins and in the production of polyimides, a class of high-temperature-resistant specialty resins used in aero-space and electrical applications.

While the present view of the chemical structure of humic substances (the organic fraction of soil and water) is that it is comprised of benzenepolycarboxylic and phenolic acids, joined by hydrogen bonds, the extent to which benzenepolycarboxylates occur naturally as "free" acids in the soil solution and in water is believed to be exceedingly small.

No standards or regulations directly or indirectly controlling these substances are known to exist.

Toxicity data exist only for acute oral exposure to trimellitic acid and trimellitic anhydride where the LD_{50} values suggest no acute exposure hazard at environmentally realistic levels. No information on general biological effects (such as carcinogenicity, mutagenicity, etc.) was found in the literature.

One study indicated the ability of trimesic, trimellitic and pyromellitic acids to significantly inhibit cis-aconitase, an enzyme of the Krebs cycle. The Krebs cycle is a cellular mechanism for obtaining and storing chemical potential energy from metabolized protein, fat and carbohydrates. This study which used an isolated enzyme preparation is only indicative of a potential for inhibition by these compounds in whole plants or animals.

From the available information it has been concluded that, although the fate and possible effects of these compounds in the environment are not characterized, the current uses of the higher benzenecarboxylates as chemical intermediates are not resulting in significant environmental release. It is recommended, however, that, prior to the initiation of any potentially dispersive new use(s), fate and effects information be obtained.

I. GENERAL INFORMATION (including production and use)

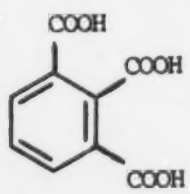
In the early 1970's, widely used phosphorus-containing detergent builders were recognized as promoters of eutrophication. (A builder is any ingredient, such as water softener, sequestering or buffering agent, that increases the detergent power of a soap or synthetic surfactant.) Use of detergent formulations employing these builders contributed significantly to water pollution problems by promoting algal growth in both municipal wastes and freshwater bodies.

Consequently, alternative builders were sought by the detergent industry. One group of compounds that has been proposed for use was the benzenepolycarboxylates. An initial literature search revealed that little was known about this group of compounds. Because of this, and because of the potential for wide dispersal in the environment should these compounds be incorporated into detergent formulations, the benzenepolycarboxylates were selected for the environmental hazard assessment series.

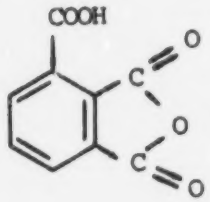
In this paper, the term "higher benzenepolycarboxylates" is used to include the benzenetricarboxylates through benzenehexacarboxylate, the chemical structures for which are shown in Figure 1. The abbreviations used herein for these compounds are also given in Figure 1. Howard and Durkin (1974) have presented a literature review on all the benzenepolycarboxylates.

Physically, these compounds are white crystalline solids or powders with high melting points and varying degrees of water solubility. Some available data for these compounds are shown in Table I. These compounds would be expected to show the chemical behavior typical to carboxylate compounds, such as the formation of water soluble alkali (sodium, potassium) and ammonium salts, and the conversion to acid chlorides, esters, amides, and, where the carboxylic acid groups are ortho to each other on the ring, anhydrides.

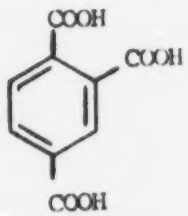
Figure 1. Chemical Structures of the Higher Benzenepolycarboxylates



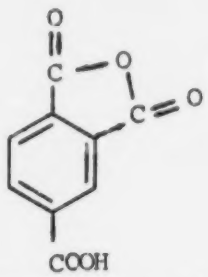
Benzene-1,2,3-tricarboxylic acid
Hemimellitic acid
(HMA)



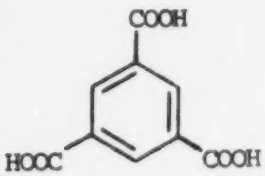
Benzene-1,2,3-tricarboxylic acid, 1,2-dianhydride
Hemimellitic anhydride
(HMAN)



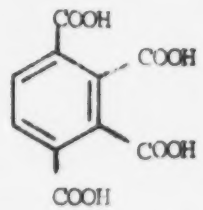
Benzene-1,2,4-tricarboxylic acid
Trimellitic acid
(TMA)



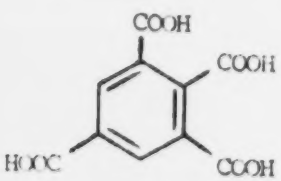
Benzene-1,2,4-tricarboxylic acid, 1,2-dianhydride
Trimellitic anhydride
(TMAN)



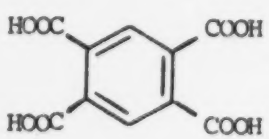
Benzene-1,3,5-tricarboxylic acid
Trimesic acid
(TMSA)



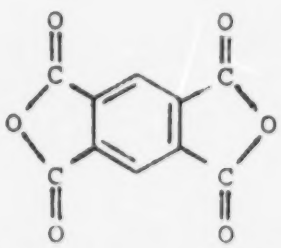
Benzene-1,2,3,4-tetracarboxylic acid
Mellophanic acid



Benzene-1,2,3,5-tetracarboxylic acid
Prehnitic acid

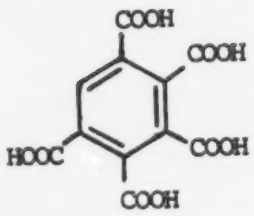


Benzene-1,2,4,5-tetracarboxylic acid
Pyromellitic acid
(PMA)

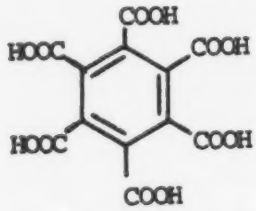


Benzene-1,2,4,5-tetracarboxylic acid, dianhydride
Pyromellitic dianhydride
(PMDA)

Figure 1. (cont.)



Benzenepentacarboxylic acid



Benzenehexacarboxylic acid
Mellitic acid
(MA)

Table I - Some Available Physical Data for the Higher Benzenepolycarboxylates

	BP(°C)	MP(°C)	Solubility (g/100g solvent) Water	Methanol(m)/Ethanol(e)	Xylene	CCl_4
Hemimellitic Acid	--	190-197 (decomp)	--	--	--	--
Hemimellitic Anhydride	--	197	--	--	--	--
Trimesic Acid	--	375-380 (subl)	0.24 (25°C)	8.0(m) (25°C)	0.01 (o-xylene)	0.01
Trimellitic Acid	--	216-218	2.1 (25°C)	25.3(e) (25°C)	0.006	0.004
Trimellitic Anhydride	390	168	(reacts)	(reacts)	0.4	0.002
Pyromellitic Acid	--	257-265 (decomp)	1 (20°C)	10(e) (10°C)	--	--
Pyromellitic Dianhydride	397-400	287	--	--	--	--
Mellitic Acid	--	286-288 (decomp)	Sol.	Sol.	--	--

These compounds are manufactured by oxidation of the polymethylbenzene analogs using air, nitric acid, or chromic acid as the oxidizing agent (Towle et al., 1968). Of the higher benzenepolycarboxylates, only trimesic acid, trimellitic acid (and its anhydride), and pyromellitic acid (and its dianhydride) have known current commercial significance. Because these compounds are produced by fewer than three companies, no production figures may be reported by the International Trade Commission. Table II lists the three commercially significant compounds.

Trimellitic anhydride is used to prepare plasticizers, alkyd resins, unsaturated polyesters, printing inks, resin intermediates, adhesives, molding resins and dyes. The largest outlet is the preparation of its triisooctyl and triisodecyl esters, which are used as specialty plasticizers in vinyl resins where permanency is required (as in wire insulation, upholstery, refrigerator gasketing and thin fabric coatings). Production of trimellitic acid esters has increased steadily from 0.88 million pounds in 1963 to 15.4 million pounds in 1973, the latter requiring between 5.4 and 6 million pounds of TMAN. Other major applications of TMAN include the production of poly(amide-imide) resins for use in wire enamels and electric-insulating varnishes; poly(ester-imide) formulations used for wire enamels; and water-based alkyd resins used in the surface coatings industry (Stanford Research Institute, 1971; 1972; 1974).

Toward the end of the 1960's, trimesic acid was reported to have been under development for commercial use as a crosslinking agent for polymers, and in the preparation of triester plasticizers (Towle et al., 1968). However, in an oral communication with American Bio-Synthetics Corporation (1974), it was learned that the only current commercial use of TMSA is as a crosslinking agent in solid propellant fuels.

Pyromellitic dianhydride (PMDA) is used as a crosslinking and curing agent for epoxy resins which, in turn, are used for

Table II - Producers of the Commercially Significant Higher Benzenepolycarboxylates

Product	Producer	Capacity* (Million of Pounds)
Trimesic Acid	American Bio-Synthetics Corp. (Milwaukee, Wisc.)	--
Trimellitic Anhydride	Amoco Chem. Corp. (Joliet, Ill.)	50 (in 1969)
Pyromellitic Acid (and dianhydride)	1. E.I. DuPont de Nemours & Co. Inc., Indust. Chem. Dept. (Gibbstown, N. J.)	3-4 (in 1971)
	2. Princeton Chem. Research Inc. (Princeton, N. J.)	0.4 (in 1965)

*Stanford Research Institute, 1971

protective surface coatings, adhesives and a number of other applications. Combined with aromatic diamines, PMDA is used to produce polyimides of excellent high-temperature resistance. PMDA-based polyimides are specialty resins used in such applications as electrical sheet and film insulation, laminates, electrical wire coatings, and varnishes, diamond abrasive wheels, precision parts, and for various aerospace applications (Stanford Research Institute, 1971). Pyromellitic acid is described in a patent as the active ingredient in dental plaque-inhibiting mouthwash, toothpaste and toothpowder preparations (Felger, Gillette Co., 1972). The patent office of the Gillette Company reported that the PMDA dentifrice preparation is still a "paper patent", i. e., there is no commercial use of these products, but that the National Institute of Dental Research has expressed interest in testing PMDA in its anti-plaque/anti-caries drug investigations (Anderson, 1975).

In a patent for a nitrogen- and phosphorus-free detergent formulation, hexasodium benzenehexacarboxylate and pentasodium benzenepentacarboxylate are named as the primary detergent builders, with the sodium salts of tri- and tetracarboxylates as additional builders (Benjamin and Sayler, Procter and Gamble, 1973). A second patent, although naming only tetrasodium benzenetetracarboxylate as the detergent builder, describes a typical composition which includes as a builder at least one C_{1-8} aliphatic or aromatic carboxylate or anhydride, or its ammonium or alkali metal salt at a concentration of 2 percent by weight (Hentschell and Hentschell, 1973).

While the proposed use of the higher benzenepolycarboxylates as detergent builders was instrumental in initiating this environmental hazard assessment, a recent oral communication with a Procter and Gamble representative (Hall, 1975) disclosed that benzenepentacarboxylate and benzenehexacarboxylate, while found to be satisfactorily biodegradable, were not adequate as detergent builders. There has been no attempt to market the benzenepolycarboxylates as detergent builders to date by Procter and Gamble, or, as far as can be determined, by any other detergent formulator.

II. ENVIRONMENTAL ASPECTS

No monitoring data or background level measurements are known to exist for these compounds. While no analytical method specifically designed for detection of the higher benzenepolycarboxylates in the environment has been reported in the literature, Schnitzer and others working with humic substances have made extensive use of gas chromatography to identify benzenepolycarboxylates (usually as the more volatile methyl esters) in degraded humic and fulvic acids (Schnitzer and Khan, 1972). The method should be adaptable for detecting benzenepolycarboxylates in other environmental samples.

To date, the higher benzenepolycarboxylates have not been identified or implicated as environmental contaminants. No incidents of losses to the environment from their manufacture, transport, or use in the production of other substances have been reported.

As is the case for many chemical intermediates, entry into the environment via decomposition of the end products is possible; however, there are no reports describing such an occurrence regarding the higher benzenepolycarboxylates.

It does not appear that the higher benzenepolycarboxylates occur naturally as the acids. However, the chemical nature of humic substances (the bulk of the organic matter in soil and water) is currently viewed as being composed of benzenepolycarboxylic and phenolic acids held together by hydrogen bonds to form a stable polymeric structure. Weakening of these bonds will break the structure and release the component parts. All of the benzenepolycarboxylates have been identified as products of humic substances from various soils treated with permanganate, nitric acid, or by a non-degradative method involving methylation with diazomethane (Schnitzer and Khan, 1972). The extent to which the

benzenepolycarboxylates occur in humic substances as the "free" acids is not known, but is thought to be exceedingly small (Schnitzer, 1975).

According to Poole (1975), benzenepentacarboxylate and benzene-hexacarboxylate were found to be quite biodegradable using a 26-day carbon dioxide production test (see Sturm, 1973) and a BOD test. While degradation appears probable, and incorporation into humic substances possible, the mobility and ultimate fate of higher benzenepolycarboxylates in the environment is not adequately understood.

There are no known standards, regulations or guidelines to control the higher benzenecarboxylates.

III. BIOLOGICAL ASPECTS

1. Toxicity

The only toxicity data encountered in the literature dealt with the acute toxicity of trimellitic acid and the corresponding anhydride. The oral LD_{50} of TMA was determined to be 1.25 g/kg in mice and 1.90 g/kg in rats, while TMAN was found to have an LD_{50} of 2.50 g/kg in mice and 6.25 g/kg in rats. In both rats and mice, oral administration of TMA and TMAN elicited the same basic symptoms: swelling of internal organs and skin, and respiratory depression. Inhaled TMA seems primarily to attack the mucous membranes, causing signs of respiratory distress (Batyrova and Uzhdavini, 1970).

The LD_{50} values for TMA and TMAN reported above indicate that they are at most only moderately toxic under conditions of acute exposure and that the levels necessary to cause acute adverse effects are, for these two compounds, environmentally unrealistic. No chronic toxicity studies, studies of carcinogenicity, mutagenicity, etc., were found, nor was any information found dealing with aquatic toxicity, phytotoxicity or toxicity to microorganisms.

2. Metabolic Effects, In vitro

Gavron and Birckbichler (1971) found that trimesic acid, trimellitic acid and pyromellitic acid competitively inhibit the enzyme cis-aconitase, isolated from pig heart. Table III shows percentages inhibition for these compounds and for three benzenedicarboxylates. cis-Aconitase is an enzyme which converts citrate to isocitrate in the Krebs cycle. The Krebs cycle is the biochemical pathway present in animal and plant cell mitochondria through which fragments of organic compounds, available from various metabolic reactions involving the degradation of proteins, fats and carbohydrates, can be effectively utilized to obtain and

TABLE III.

Inhibition of cis-Aconitase by
Various Benzenepolycarboxylic Acids at mM

Acid	% Inhibition
Terephthalic	0
Isophthalic	3
Phthalic	5
Trimesic	20
Trimellitic	33
Pyromellitic	51

store chemical potential energy. Interference with the Krebs cycle is, therefore, a serious threat to the organism. Demonstration of *in vitro* inhibition, as described above, does not imply that these compounds will interfere with the Krebs cycle *in vivo*, where absorption, metabolism, transport to the mitochondria and other factors need to be considered. At the same time, the information does indicate a potential for this metabolic effect to occur in whole plants and/or animals.

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